Functional sarcoplasmic reticulum for calcium handling of human embryonic stem cell-derived cardiomyocytes: insights for driven maturation.

Journal: Stem Cells

Publication Year: 2007

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PubMed link: 17872499

Funding Grants: Stem Cell Research Training Grant

Public Summary:

Scientific Abstract:
Cardiomyocytes (CMs) are nonregenerative. Self-renewable pluripotent human embryonic stem cells (hESCs) can differentiate into CMs for cell-based therapies. In adult CMs, Ca(2+)-induced Ca(2+) release from the sarcoplasmic reticulum (SR) via the ryanodine receptor (RyR) is key in excitation-contraction coupling. Therefore, proper Ca(2+) handling properties of hESC-derived CMs are required for their successful functional integration with the recipient heart. Here, we performed a comprehensive analysis of CMs differentiated from the H1 (H1-CMs) and HES2 (HES2-CMs) hESC lines and human fetal (F) and adult (A) left ventricular (LV) CMs. Upon electrical stimulation, all of H1-, HES2-, and FLV-CMs generated similar Ca(2+) transients. Caffeine induced Ca(2+) release in 65% of FLV-CMs and approximately 38% of H1- and HES2-CMs. Ryanodine significantly reduced the electrically evoked Ca(2+) transient amplitudes of caffeine-responsive but not -insensitive HES2- and H1-CMs and slowed their upstroke; thapsigargin, which inhibits the sarco/endoplasmic reticulum Ca(2+)-ATPase (SERCA) pump, reduced the amplitude of only caffeine-responsive HES2- and H1-CMs and slowed the decay. SERCA2a expression was highest in ALV-CMs but comparable among H1-, HES2-, and FLV-CMs. The Na(+)-Ca(2+) exchanger was substantially expressed in both HES2- and H1-CMs relative to FLV- and ALV-CMs. RyR was expressed in HES2-, H1-, and FLV-CMs, but the organized pattern for ALV-CMs was not observed. The regulatory proteins junctin, triadin, and calsequestrin were expressed in ALV-CMs but not HES2- and H1-CMs. We conclude that functional SRs are indeed expressed in hESC-CMs, albeit immaturely. Our results may lead to driven maturation of Ca(2+) handling properties of hESC-CMs for enhanced contractile functions. Disclosure of potential conflicts of interest is found at the end of this article.